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PATHOLOGICAL REPORT ON A CASE OF RABIES IN A WOMAN.

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GENERAL REMARKS.

While walking through a vacant lot on February 11, 1902, Mrs. J., colored, of Washington, D. C., was fiercely attacked and severely bitten on the right forearm, near the inner canthus of the left eye, and on the left frontal eminence by a stray collie dog. Eighteen days later the woman complained of a general malaise and pains in the cicatrized wounds of the head, which rapidly grew more severe, necessitating the services of a physician. Upon the latter's advice the patient was removed on the following day to Freedmen's Hospital, where the case was diagnosed as "suspected rabies." On the afternoon of March 3 the writer visited the hospital, on the invitation of Dr. William C. Woodward, District health officer, to whom we are indebted for the kindness of having brought this case to our attention. The patient was found in an extremely nervous condition, having an excessive feeling of fear and uneasiness. The eyes were staring, and a general expression of anxiety pervaded the countenance of the individual. The mind, however, was clear and no efforts at violence were made. When interviewed as to the cause of the scars on her head and forearm, she lightly replied: "Oh, a dog bit me there some weeks ago, but they are all right now."

From time to time reflex spasms involving the muscles of deglutition were noticed, causing a clutching at the throat and difficult breathing during the attack. These rapidly became more generalized, and in a few hours also involved the respiratory muscles, causing extreme dyspnea. Attempts at vomiting would then occur, but no evacuations followed. Contrary to the usual run of cases, the patient accredited these symptoms to indigestion and had not the slightest suspicion of the true nature of her condition, thus disproving the idea that the nervousness and fear usually seen in the early stages of rabies in the human subject are due to the natural dread of the disease and appre-

^aThis report was prepared for filing in the District Health Office, together with the records furnished by the attending physician, the hospital pathologist, and the resident physician. For this reason only those portions of the history and clinical symptoms that were brought to my attention will be given at this time.—J. R. M.

hension of the consequence rather than to organic changes in the central nervous system.

During the night these symptoms became more aggravated, and spasms followed one another more rapidly, causing grave delirium. The patient finally became violent, and necessitated the adoption of forcible measures to keep her under control. Death occurred on the following day, March 4, twenty-one days after the bites had been inflicted, and a postmortem examination was made by the hospital pathologist at noon. The cadaver showed a well-developed female about twenty-eight years of age. The heart, lungs, spleen, liver, kidneys, stomach, and intestines were apparently normal. The meninges of the brain were somewhat injected and the brain substance slightly edematous. Macroscopic examination of these tissues failed to reveal any pathological lesions which could be held accountable for the symptoms which resulted in death.

Following the necropsy, the medulla oblongata, the superior portion of the spinal cord, and the right plexiform ganglion of the pneumogastric nerve were removed under aseptic precautions, placed in sterile flasks, and brought to the Pathological Division of the Bureau of Animal Industry for an investigation of rabies.

A series of culture media consisting of peptonized beef bouillon, slant and stab agar, gelatin, blood serum, and fermentation tubes of saccharose, lactose, and glucose were inoculated from the center of the medulla oblongata, after searing the surface and making a transverse incision with a flamed knife. The absence of microorganisms was demonstrated by the failure of any of these various media to show fertility.

HISTOLOGICAL EXAMINATION.

A histological examination of the plexiform ganglion was made for the purpose of determining whether the lesions described by Van Gehuchten and Nelis^a as typical of rabies were present. After fixation in a 10 per cent solution of formalin, it was transferred to 95 per cent alcohol, then to absolute alcohol, each for a period of two hours, placed in equal parts of alcohol and chloroform for one hour, chloroform one hour, chloroform and paraffin one hour, and paraffin six hours. The sections were stained in hematoxylin and eosin, Unna's polychromatic blue, and Van Gieson's picric acid and acid fuchsin. On microscopic examination, instead of finding the ganglion composed of the normal ganglionic cells surrounded by their capsules, consisting of a single layer of endothelial cells and situated in the interstitial neuroglial tissue (see Pl. 1, fig. 1), a very different picture was observed. The large majority of the ganglion cells were found to be affected, but in varying degrees of intensity. (See Pl. 1, fig. 2.)

^aDiagnostic histologique de la rage, A. Van Gehuchten and C. Nelis, *Annales de Médecine Vétérinaire*, v. 49, Mai 1900, pp. 243-252.

The principal change observed was the extensive proliferation of the layer of endothelial cells of the capsule, although the leucocytic infiltration of the sustentacular tissue was also well marked. This proliferation and ingrowth of new cells from the capsule had invaded the pericellular spaces and the protoplasm of a number of the nerve cells and produced pressure on, and consequent atrophy of, the cytoplasm, thus leaving the nucleus surrounded by several layers of proliferated endothelial cells. In a few ganglion cells the pathological process had extended still further, causing a complete obliteration of the nucleus as a result of the invasion of the entire capsule by a dense mass of cells, causing these areas to assume a decidedly sarcomatous aspect. In other cells the changes were but slightly marked, the only observable alteration being an increase in the number of endothelial cells lining the capsule, the faint cell nuclei, or the poorly stained cellular protoplasm.

A portion of the medulla in the region of the apex of the corpora pyramidalia was fixed in the usual manner. After thorough dehydration in absolute alcohol the tissue was placed in a thin solution of celloidin for twelve hours, then into thick celloidin for an equal length of time. Sections were stained with alum hematoxylin and eosin, Van Gieson's picric acid and acid fuchsin, and Nissl's stains. The lesions observed were in part similar to the description given by Babes,^a but not so extensive. A well-marked accumulation of embryonic cells about the blood vessels in the perivascular lymph spaces was seen and a leucocytic infiltration also observed surrounding some of the ganglion cells. These perivascular and periganglionic cell accumulations have been termed by Babes the "rabid tubercles," and are considered by him as diagnostic. Some of the blood vessels appeared dilated with an extensive proliferation of connective tissue cells of the adventia. The changes of the ganglion cells were not so marked. Disseminated swelling and disintegration of the Nissl bodies (chromatolysis) were present in some cells, while in others only tumefaction could be seen, with the cytoplasm taking the stain but feebly. In teased preparations the processes of the nerve cells appeared more or less distorted and atrophied, and vacuolation was occasionally observed. The latter was also manifest at times in the cells of the neuroglia.

INOCULATION EXPERIMENTS.

Within three hours from the time of removing the medulla from the cadaver (4 p. m., March 4, 1902), an oblongata emulsion had been injected into eight rabbits. This species of animal was used owing to

^a "Sur certains caractères des lésions histologiques de la rage," by V. Babes (*Annales de l'Institut Pasteur*, v. 6, No. 4, Apr., 1892, pp. 209-223).

"Rapid diagnosis of rabies by the examination of the bulb of the biting dog," by V. Babes, *Vet. Jour.*, v. 51, No. 303, Sept., 1900, pp. 158-160.

their well-known susceptibility, and also on account of the classic symptoms produced after the development of the disease.

A cube about 1 centimeter in each dimension was removed aseptically from the bulb and placed in a sterile mortar, where it was thoroughly macerated into a homogeneous mass before the addition of sufficient physiological salt solution to give the emulsion the appearance of baker's yeast. The supernatant liquid was then drawn into the syringe and injected into full-grown rabbits averaging 1,280 grams in weight. Several methods of injection were followed in order to dispel, if possible, skepticism based upon inoculations that are made into the cephalic cavity. For this and other reasons two rabbits were injected with 0.5 c. c. of the emulsion into the substance of the splenius muscle in the posterior auricular region. Two others received 0.75 c. c. of the material in the great dorsal muscle at a point superior to the scapula. The remaining four animals were inoculated with 0.1 c. c. of the emulsion by trephining the frontal bone. In two (Nos. 66 and 67) a disk of bone was removed and the emulsion injected subdurally after the method of Pasteur. The other two (Nos. 64 and 65) were injected intracerebrally following the method advocated by Leclainche and Morel.^a

In all these cases the usual method of procedure was adopted, namely, clipping off the hair, washing the seat of operation with a 5 per cent solution of carbolic acid, rinsing with sterile water, and then inoculating after the animals had been thoroughly anesthetized with ether. Following the inoculations, the animals recovered nicely from the effects of the anesthetic and the next day were as bright and as lively as at any previous time. As a control on this experiment, and in order to give further evidence that normal brain tissue will not produce rabiform symptoms, two rabbits were injected as checks with normal brain tissue—one by the intracerebral method and the other by inoculating into the great dorsal muscle. All the animals were placed under daily supervision, and it was noted that the operation wounds healed quickly by first intention. Not until the fourteenth day (March 18) was anything unusual observed, and on this day it was found that rabbits Nos. 65 and 67 refused their food; otherwise they appeared perfectly well. Temperatures were not taken at any time, as it was not desired to subject the animals to any unusual or exciting conditions. On the fifteenth day the rabbits previously mentioned showed symptoms of nervousness and irritability. When a stick was thrust at No. 65, attempts at biting it were made. On this date rabbits Nos. 64 and 66 showed anorexia.

Sixteenth day: Nos. 65 and 67 appeared dull and languid and remained crouched up, with respirations accelerated. Rabbit No. 64 showed the hyperesthetic condition noticed in the first two animals the

^a "Inoculation intra-cérébrale du virus rabique," by Leclainche and Morel, *Annales de Médecine Vétérinaire*, v. 49, 1900, pp. 88-89.

previous day, while No. 66 had evidently passed that stage and appeared stupid, with eyes half closed. During the morning it was crouched up in the corner of the cage, and at 4 p. m. was lying down, partially paralyzed.

Seventeenth day: No. 66 was found dead. Nos. 65 and 67 were partially paralyzed, but they could at times move about their cage. The former had two convulsions during the morning, and in the afternoon the convulsions became more frequent—one about every twenty minutes. At 4 p. m. this rabbit went down on its side with opisthotonos, and occasional attempts to recover its equilibrium were made. At noon, No. 65 lay prone on its belly, with forefeet outstretched and hind legs extended, without ability to recover itself. Masticatory movements were observed, with gritting of the teeth. At 4 p. m. No. 67 was likewise prostrate on its side, with head thrown back, and occasional efforts were made at locomotion. No. 64 remained very nervous, and frequently endeavored to burrow through the iron floor of the cage.

Eighteenth day: At 9 a. m. breathing could scarcely be noticed in No. 65. Death occurred one hour later. No. 67 remained in about the same position as the previous evening, but more enfeebled, with respirations almost imperceptible shortly after noon. Death occurred about 3 p. m. Rabbit No. 64 appeared dull and languid.

Nineteenth day: Rabbit No. 64 was found on its side, with opisthotonos and accelerated respirations.

Twentieth day: Rabbit No. 64 died during the night. Nos. 70 and 71 had no desire for food, but did not show any other indications of illness.

Twenty-first day: The two last-mentioned animals seemed to be easily excited, and on opening the cage made attempts at hiding their heads under their fellows. In the afternoon they appeared dull and listless. No. 69 showed anorexia.

Twenty-second day: At 9 a. m. the latter animal showed extreme lassitude, and was partially paralyzed by 4 p. m. No. 68 ate sparingly of its food.

Twenty-third day: No. 69 was found dead this morning, No. 70 completely paralyzed, and No. 71 died during the afternoon. No. 68 appeared hypersensitive.

Twenty-fourth day: No. 70 died. No. 68 did not develop further symptoms than those exhibited the previous day.

Twenty-fifth day: The latter animal was very languid, becoming totally paralyzed on the twenty-seventh and dying on the twenty-eighth day.

In order to exclude any intercurrent disease as the cause of death in these rabbits, various culture media were inoculated in the majority of cases from all the organs, including the brain. In but one instance (the liver of No. 66) did the medium become fertile, and this was an

obvious contamination probably due to the length of time the animal had been dead before making cultures. This negative evidence is of little value except incidentally to support the diagnosis of rabies. Postmortem examinations were made in all cases and the brain carefully examined, but, except a slight congestion or edema of the latter organ, no perceptible lesions were observed that could be held accountable for the symptoms produced. To obtain still more conclusive evidence, and to eliminate to even a greater degree the possibility of extraneous infection, a subseries of inoculations was made on March 22 by injecting 0.1 c. c. of a medulla emulsion from Nos. 67 and 65 intracerebrally into rabbits Nos. 212 and 211, respectively; 0.75 c. c. of a similar material from the brain of No. 69 was inoculated into the great dorsal muscle above the scapula of rabbit No. 281 on March 27. These animals were as lively the following day as usual, and did not develop any untoward symptoms until the thirteenth, fifteenth, and seventeenth day, respectively. The symptoms started in the same manner as was described for the first series, and ran approximately the same course, the rabbits dying on the sixteenth, seventeenth, and twenty-first day, respectively. The postmortem examination of these animals and culture-media inoculations from their viscera proved negative.

The following table will give a summary of results in a more convenient form for comparison:

Results of inoculation experiments for rabies.

Rabbit No.	Method of inoculation.	Dose injected.	Source of material injected.	Date injected.	Date of first symptom.	Date of death.	Period from inoculation to death.	Diagnosis.
First series:		c. c.					Days.	
64.....	Subdurally	0.1	Medulla, Mrs. J	Mar. 4	Mar. 19	Mar. 24	20	Rabies.
65.....do1dodo ..	Mar. 18	Mar. 22	18	Do.
66.....	Intracerebrally...	.1dodo ..	Mar. 19	Mar. 21	17	Do.
67.....do1dodo ..	Mar. 18	Mar. 22	18	Do.
68.....	Intramuscularly .	.5dodo ..	Mar. 23	Apr. 1	28	Do.
69.....do5dodo ..	Mar. 25	Mar. 27	23	Do.
70.....do75dodo ..	Mar. 24	Mar. 28	24	Do.
71.....do75dododo ..	Mar. 27	23	Do.
Subinoculations:								
211.....	Intracerebrally...	.1	Brain rabbit No. 67.	Mar. 22	Apr. 6	Apr. 8	17	Do.
212.....do1	Brain rabbit No. 65.do ..	Apr. 4	Apr. 7	16	Do.
281.....	Intramuscularly .	.75	Brain rabbit No. 71.	Mar. 27	Apr. 13	Apr. 17	21	Do.
Checks:								
72.....	Intracerebrally...	.1	Normal brain tissue.	Mar. 4	(a)
73.....	Intramuscularly .	.75dodo ..	(a)

• Apparently healthy.

It will be seen from the above table that the rabbits inoculated with the oblongata emulsion from Mrs. J. have all succumbed with unmistakable and characteristic symptoms of rabies. Also that the three rabbits in the subseries likewise developed the typical paralytic form of rabies. Further, that the two check rabbits are still alive and their health apparently unimpaired at this writing.^a As a result of the microscopic lesions found by the histological examination of the plexiform ganglion on the pneumogastric nerve and of the bulb of the medulla, also of the experimental inoculation of rabbits, it seems justifiable to conclude that the person in question was suffering with rabies at the time of death.

^aThese animals were chloroformed eight months after inoculation and found to be in a healthful condition.

DESCRIPTION OF PLATE I.

Fig. 1. Section of normal plexiform ganglion stained with hematoxylin and eosin. Camera-lucida drawing made at the stage level with No. 4 compensating ocular and Zeiss 4 mm. objective.

Note the single layer of endothelial cells (*a*) lining the capsule of the ganglionic cells, the open pericellular space, and the appearance of the protoplasm and nuclei of the nerve cells (*b*).

Fig. 2. Section of the plexiform ganglion of Mrs. J. stained with hematoxylin and eosin. Camera-lucida drawing made at stage level with No. 4 compensating ocular and Zeiss 4 mm. objective.

The proliferation of the endothelial cells of the lining capsule (*a*) is well marked, as is also the destruction of the cell protoplasm (*b*) and the infiltration of leucocytes (*c*).

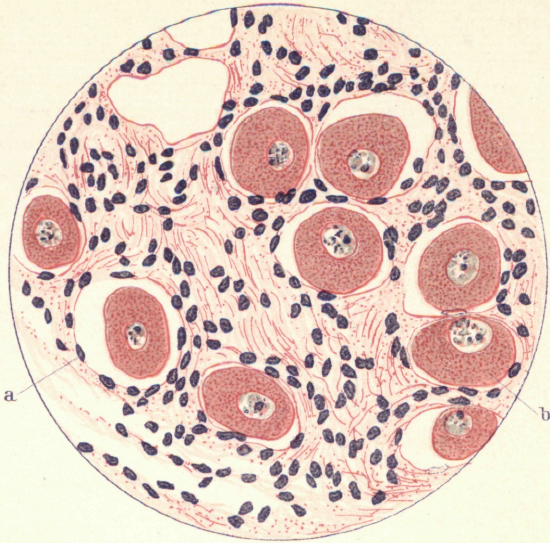


FIG. 1.—SECTION OF NORMAL NERVE GANGLION.

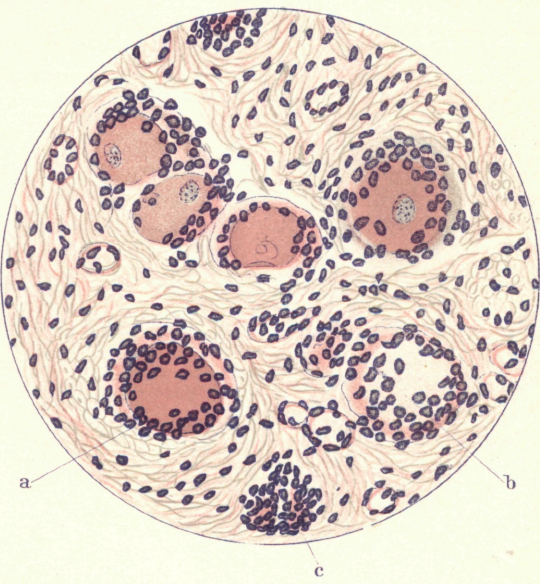


FIG. 2.—SECTION OF GANGLION SHOWING LESIONS OF RABIES.